alpha-Ketoglutarate Accelerates the Initial Differentiation of Primed Human Pluripotent Stem Cells.

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Public Summary:
Induced stem cells can stay stem cells or differentiate into more mature cells and adult cells depending on the specific culture conditions. We have found that a specific gene, alphaketogluterate that is normally involved in cellular metabolism, is in charge of determining whether the cell stays a stem cell or differentiates into an adult cell.

Scientific Abstract:
Pluripotent stem cells (PSCs) can self-renew or differentiate from naive or more differentiated, primed, pluripotent states established by specific culture conditions. Increased intracellular alpha-ketoglutarate (alphaKG) was shown to favor self-renewal in naive mouse embryonic stem cells (mESCs). The effect of alphaKG or alphaKG/succinate levels on differentiation from primed human PSCs (hPSCs) or mouse epiblast stem cells (EpiSCs) remains unknown. We examined primed hPSCs and EpiSCs and show that increased alphaKG or alphaKG-to-succinate ratios accelerate, and elevated succinate levels delay, primed PSC differentiation. alphaKG has been shown to inhibit the mitochondrial ATP synthase and to regulate epigenome-modifying dioxygenase enzymes. Mitochondrial uncoupling did not impede alphaKG-accelerated primed PSC differentiation. Instead, alphaKG induced, and succinate impaired, global histone and DNA demethylation in primed PSCs. The data support alphaKG promotion of self-renewal or differentiation depending on the pluripotent state.